

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020500/S005

MEDICAL/STATISTICAL COMBINED REVIEW(S)

**Clinical and Statistical Review of
an Efficacy Supplement:
NDA 20-500/S-005
Mepron® Atovaquone Suspension for the Prevention of
Pneumocystis carinii Pneumonia**

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LABELING

2. BACKGROUND

Proposed Package Insert Regarding Dosage and Administration for PCP Prophylaxis:

The Applicant seeks approval for a daily dosing regimen of Mepron® suspension for the prevention of PCP pneumonia and would like to include the following:

Table 1. Daily Dosing Regimen		
	Total Daily Dose	Dose Frequency
<u>Adults and Adolescents</u> (13-16 years):	oral dose is 1500 mg (10 ml)	q. day administered with a meal
<u>Pediatric Patients</u> (1 to 3 months and 2-13 years):	30 mg/kg (maximum 1500 mg)	q. day administered with a meal
(3 to 24 months):	45 mg/kg (maximum 1500 mg)	q. day administered with a meal

Reviewers' Note: Some of the following text is excerpted from the Applicant's submission. Reviewer comments will be marked as such and highlighted in italics.

Medication: Mepron® oral suspension

Atovaquone (566C80; trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone) is a hydroxynaphthoquinone with activity against *Pneumocystis carinii*, *Toxoplasma gondii* and *Plasmodium spp.* *in vitro* and in animal models.

Mepron® is indicated for the treatment of PCP infection. The adult daily dose is 750 mg bid for the treatment of PCP infection.

A. Regulatory History:

Atovaquone is indicated for the treatment of mild to moderate *Pneumocystis carinii* pneumonia (PCP) in patients with acquired immunodeficiency syndrome (AIDS) who are intolerant to trimethoprim/sulfamethoxazole (TMP/SMX). The studies that demonstrated the safety and efficacy of atovaquone were conducted with the tablet formulation and the results of those studies have been submitted previously (NDA 20-259, approved for marketing 24 November 1992 at a dose of 750 t.i.d. x 21 days.) Those studies showed that there is a close correlation between steady-state plasma concentration and clinical efficacy. Those studies also showed that the bioavailability of atovaquone when administered as the tablet formulation is limited and, as a result, some patients have subtherapeutic concentrations of atovaquone after dosing.

Subsequent studies showed that the bioavailability of atovaquone is greatly enhanced when administered as a microfluidized suspension with smaller particle size. Mepron® suspension IND was submitted on Oct 22, 1992. The NDA to

demonstrate bioequivalence of Mepron® tablets and suspension was submitted on Aug 15, 1994 (20-500). Results of studies that identified 750 mg twice daily for 21 days as the appropriate dose of atovaquone suspension for treatment of mild to moderate PCP in patients intolerant to TMP/SMX have been submitted previously (NDA 20-500, approved for marketing 8 February 1995). The label of the suspension points out that the suspension provides an approximately two-fold increase in bioavailability in the fasting or fed state compared to the previously marketed tablet. Mepron® tablet is no longer marketed. Mepron® tablets have been withdrawn from the market in favor of the suspension in those countries where the suspension is approved for the same indication. Mepron® suspension is approved for a PCP treatment indication in 16 other countries.

The US is the first country for which the prophylaxis indication is being sought. A pre-NDA meeting was held on Sept 24, 1997. The previous MOs who worked on this project were Drs. Mann & Bimkrant. Executive summary of results of protocol 211 were made available by the sponsor to the FDA via a teleconference on Mar 27, 1997. It was determined that study 115-213 should be discontinued; this was because enrollment was slower than expected and discontinuation was higher than expected. The study report for study 115-213 explicitly states that there were no safety issues involved in the decision to recommend termination.

Mepron® was granted orphan status Aug 14, 1991 for prevention of PCP in high risk, HIV infected patients as defined by one or both of the following:

- history of one or more episodes of PCP, and
- CD4 count $< 200/\text{mm}^3$.

B. Background on PCP Rx and Prophylaxis

Pneumocystis carinii pneumonia is the most common opportunistic infection (OI) and life-threatening disease in HIV-infected patients. Before the widespread use of PCP prophylaxis, most North Americans with acquired immunodeficiency syndrome (AIDS) had one or more episodes of PCP during the course of their HIV infection. In 1992, a U.S. Public Health Service task force¹ identified the following as risk factors for PCP:

- CD4+ cell count $< 200 \text{ cells}/\text{mm}^3$;
- Constitutional symptoms (e.g., thrush or unexplained fever $> 100^\circ \text{F}$ for 2 weeks);
- A history of PCP.

The task force recommended that patients with any of these risk factors receive PCP prophylaxis and that prophylaxis for these patients be continued throughout their lifetimes. Subsequent to the widespread use of PCP prophylaxis, the morbidity and mortality associated with PCP declined and, because patients could be treated earlier and on an outpatient basis, the expense of the disease decreased. This highlights the need for identification of appropriate prophylaxis for all patients who are at risk.

There are two approved therapies for prophylaxis of PCP: TMP/SMX and aerosolized pentamidine. It is generally agreed that TMP/SMX is more effective but less well tolerated than aerosolized pentamidine for prophylaxis of PCP.

Although aerosolized pentamidine (AP) is approved by the FDA for PCP prophylaxis, results from a recent AIDS Clinical Trials Group (ACTG) study² indicate

that daily administration of trimethoprim/sulfamethoxazole (T/S) is more effective than AP for secondary PCP prophylaxis. Recurrence rates for patients receiving T/S were 3.5 percent and, for patients receiving AP, 18.5 percent. However, T/S is associated with allergic manifestations and side effects that limit its use, and patients who are intolerant of T/S require an effective alternative.

The limitations of AP (high relapse and failure rates, high cost, and difficulties related to administration) have led clinicians to seek an alternative for PCP prophylaxis in T/S-intolerant patients.

Dapsone and atovaquone are two promising alternatives to AP for patients who are T/S intolerant. Several studies have investigated the efficacy of dapsone for PCP prophylaxis.^{3,4,5,6,7} These studies demonstrated that dapsone is effective for PCP prophylaxis and has relatively few side effects. In addition, because it has a long half-life, dapsone requires infrequent dosing which may enhance patient compliance.

In November 1992, atovaquone was approved for the treatment of mild to moderate PCP in patients who are intolerant of T/S. Atovaquone is effective as a treatment for PCP⁸, and it is tolerated better than pentamidine⁹. The efficacy of atovaquone is directly related to drug concentrations in plasma, and there is a 95 percent therapeutic success rate with a steady-state plasma concentration of 15 to 20 $\mu\text{g/mL}$. The dose of atovaquone used in this protocol will achieve plasma concentrations within this range.

Dapsone

Dapsone is a sulfone that competes with para-aminobenzoic acid (PABA) in the synthesis of folic acid. It is well absorbed when taken orally. Peak serum concentrations are reached in 4 to 8 hours, with a half-life of 10 to 50 hours (28-hour average). Dapsone is approved for the treatment of leprosy.

Hemolysis, increased methemoglobin, average hemoglobin decrease of 1-2 g/dL, increased reticulocytes, and a shortened red-cell life span are common complications of therapy with dapsone (especially in patients with G6PD deficiency, methemoglobin reductase deficiency or hemoglobin M). Other toxicities include nausea, vomiting, abdominal pain, vertigo, blurred vision, tinnitus, insomnia, fever, headache, psychosis, phototoxicity, tachycardia, albuminuria, the nephrotic syndrome, hypoalbuminemia without proteinuria, renal papillary necrosis, male infertility, drug-induced lupus erythematosus, and an infectious mononucleosis-like syndrome.¹⁰

In one study, dapsone prophylaxis was given to 156 patients with AIDS-related complex (ARC) or a history of PCP.¹¹ Only one patient developed PCP. By contrast, 14 of 19 patients who refused dapsone prophylaxis developed PCP. Anemia requiring transfusion was the major adverse experience in patients who received dapsone.

In a retrospective review, Kemper et al.¹² obtained data from the records of 6 patients who received dapsone for primary PCP prophylaxis and 24 who received the drug for secondary prophylaxis. All but one of the patients received concurrent zidovudine (ZDV). Ten patients received a maximum dose of 100 mg of dapsone per day, while the other 20 received 50 mg per day. The data from these patients were compared with data from the records of 33 patients with prior PCP who received no prophylaxis. In the group who received dapsone, only 1 patient (who received the lower

dose) developed a recurrence of PCP, which occurred 9 months after initiation of therapy and was described by researchers as "mild." No patient who received dapsone died of PCP. In the control group, seven patients relapsed; three of the seven died of PCP. Because of the concurrent administration of ZDV, hematologic toxicities were difficult to assess. Nine patients who received dapsone required blood transfusions compared with eight in the control group. One patient who received dapsone developed pruritus, while four others developed a rash. Methemoglobin levels in the dapsone patients ranged from 1.1 to 3.7 mg/dL.

The efficacy of weekly dapsone for primary or secondary PCP prophylaxis was studied by Hughes et al.¹³ Sixty-one men with AIDS received one of three doses: 100 mg (7 men), 200 mg (50 men), or 300 mg (4 men). One patient who received 200 mg/week of dapsone for secondary prophylaxis developed PCP. Two patients developed a rash (one was later rechallenged with dapsone with no subsequent rash); two developed anemia; and one patient experienced nausea, neutropenia, headache, and elevated transaminases.

Torres et al.¹⁴ compared the efficacy and safety of oral dapsone given twice weekly with that of AP given every 2 weeks for both primary and secondary prophylaxis of PCP. Over half of the study participants also received ZDV. Of 107 patients who received AP, 12 developed PCP at a mean of 30.4 weeks, while 8 of 86 patients who received dapsone developed PCP at a mean of 32.5 weeks. Patients in both study arms experienced anemia requiring transfusions at approximately an equal rate. Patients who received AP complained of cough, dizziness, dysgeusia (impaired taste), shortness of breath, and sore throat; patients in the dapsone arm reported rash and hepatic dysfunction. The researchers concluded that the two treatments were similar in efficacy and safety. Use of ZDV improved survival in both study arms.

In another study, Torres et al.¹⁵ compared the efficacy of oral twice weekly dapsone to AP for primary and secondary prophylaxis of PCP. Patients with AIDS or advanced ARC (278 individuals) were randomized to one of two treatment regimens: 100 mg oral dapsone twice weekly or 100 mg aerosolized pentamidine every week for 4 weeks and every 2 weeks thereafter. The study showed that the two regimens have similar efficacy in primary and secondary prophylaxis of PCP; 14 percent (15 of 105) of patients who received AP and 18 percent (15 of 85) of those who received oral dapsone developed either confirmed or presumed PCP during 12 months of follow-up.

The efficacy and toxicity of dapsone and T/S were compared in a study conducted by Metroka et al.¹⁶ The patients were considered to be at high risk for developing PCP because of at least one of the following factors: a CD4+ cell count of < 250 cells/mm³, severe constitutional symptoms, or prior opportunistic infection. The mean CD4+ cell count for the patients at the start of the study was 142 cells/mm³, with a range of 9 to 573 cells/mm³. Dapsone 25 mg was given 4 times a day to 173 patients, while 48 patients received 1 double-strength T/S tablet twice a day; 23 patients refused prophylaxis. Of the 173 patients who received dapsone, 2 developed PCP; none of the 48 patients who received T/S developed PCP. There were 26 episodes of PCP among the patients who refused prophylaxis. In addition, patients who received dapsone experienced significantly fewer adverse experiences than those who received T/S.

Dapsone has been studied, as monotherapy and in combination with pyrimethamine, for prophylaxis of PCP. A meta-analysis of 35 randomized clinical trials of PCP prophylaxis summarizes results that demonstrate the efficacy of dapsone for prophylaxis of PCP.¹⁷ Results from 9 studies with 2243 patients showed that dapsone-based regimens have efficacy similar to aerosolized pentamidine (pooled risk ratio 0.93, 95% CI 0.72-1.19). Results from 8 studies with 1447 patients showed a trend for better efficacy with TMP/SMX compared to dapsone-based regimens (pooled risk ratio 0.61, 95% CI 0.34-1.10). Results from 14 studies with 2248 patients clearly showed that TMP/SMX is superior to aerosolized pentamidine (pooled risk ratio 0.58, 95% CI 0.45-0.75).

The largest trial evaluating dapsone for prophylaxis of PCP was ACTG 081, in which primary prophylaxis was studied in 842 patients who were randomly assigned to therapy with either TMP/SMX (1 double-strength (DS) tablet twice daily), dapsone (50 mg twice daily) or aerosolized pentamidine (300 mg once monthly).¹⁸ Patients were followed for episodes of confirmed or presumed PCP, survival, and acute toxoplasmosis. Toxicity-driven therapy switch points were defined in the protocol and a hierarchy of alternate therapy was established (dose reduction before switching, alternate systemic therapy before aerosolized pentamidine, TMP/SMX before dapsone). The mean CD4 count at enrollment was approximately 150 cells/mm³ in each group and the median duration of follow-up was 39 months.

Using intent-to-treat analyses, there were no significant differences among the three treatment arms in the overall risk of PCP, which occurred in 31% of patients assigned to the TMP/SMX arm, 30% of patients assigned to the dapsone arm, and 39% of patients assigned to the aerosolized pentamidine arm. However, there was a significant difference in treatment-limiting toxicities among the treatment arms, and this had an important impact on the interpretation of efficacy results. By the end of the study, only 21% and 25% of patients randomized to receive TMP/SMX or dapsone, respectively, were receiving the full dose of their originally assigned treatment, in contrast to 88% of patients randomized to receive aerosolized pentamidine. An analysis of confirmed episodes of PCP that occurred while patients were receiving one of the three treatments, either as originally assigned or after switching because of toxicity, is presented in Table 2. The study was designed to allow patients who could not tolerate the full dose of TMP/SMX or dapsone to be treated with a reduced dose, thus enabling collection of information on efficacy at full dose or half dose for these two drugs.

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Table 2 : Confirmed PCP in Patients Treated with TMP/SMX, Dapsone or Aerosolized Pentamidine in Study ACTG 081 (As-Treated Analysis)						
	Treatment as randomized			Treatment as randomized or after switching		
	TMP/SMX	Dapsone	Aerosolized pentamidine	TMP/SMX	Dapsone	Aerosolized pentamidine
Full dose						
Number of episodes	4	10	37	7	20	55
Patient-years	334	382	651	390	490	828
Rate per 100 pt-yrs	1.2	2.6	5.7	1.8	4.1	6.6
Half dose						
Number of episodes	0	11	—	1	18	—
Patient-years	91	97	—	113	137	—
Rate per 100 pt-yrs	0	11.3	—	0.9	13.1	—

TMP/SMX was equally effective at full dose (1 DS tablet twice daily) or half dose (1 DS tablet daily). At full dose (50 mg twice daily), the rate for dapsone was intermediate between the rates for TMP/SMX and aerosolized pentamidine, but at half dose (50 mg daily) the rate of PCP in the dapsone group was 2-fold higher than the rate for aerosolized pentamidine and 3- to 4-fold higher than the rate for full-dose dapsone. The conclusions from this study are that dapsone, at a dose of 100 mg per day, is at least as effective as aerosolized pentamidine, but a lower dose is less effective. The average elimination half-life of dapsone is 28 hours, which supports a once daily dosing schedule.

Overall conclusions from a careful review of published data are that dapsone is effective for prophylaxis of PCP, and that intent-to-treat analyses may underestimate efficacy differences between therapies, especially when there are high rates of treatment discontinuation and significant differences in the occurrence of treatment-limiting toxicities between assigned therapies. Thus, the Applicant states that although dapsone is not approved by the FDA for prophylaxis of PCP, the evidence from the literature regarding its efficacy makes it an appropriate drug to use in an active control arm of a study to evaluate the efficacy of a new agent for prophylaxis of PCP.

Pyrimethamine and Folinic Acid with Dapsone

As the incidence of PCP is declining because of effective prophylactic regimens, the incidence of toxoplasmosis appears to be increasing. A study conducted by Girard and colleagues¹⁹ compared the combination of dapsone and pyrimethamine with AP alone as primary prophylaxis against PCP and toxoplasmosis in HIV-infected persons. Toxoplasmosis developed in 32 of 176 (18%) patients receiving AP and in 19 of 173 (11%) patients receiving dapsone and pyrimethamine. The relative risk of PCP was equal in both groups, but the relative risk of toxoplasmosis was higher for persons receiving AP. Among the 262 patients with serologic evidence of past exposure to *Toxoplasma*, the relative risk for patients assigned to AP was 2.4-fold higher than that for patients assigned to dapsone and pyrimethamine. The authors concluded that the dapsone-pyrimethamine combination was as effective as AP in preventing PCP (although not as well tolerated) and more effective in preventing toxoplasmosis.

Opravil and colleagues²⁰ conducted a comparative study of once weekly dapsone (200 mg) and pyrimethamine (75 mg) versus AP 300 mg administered every 4 weeks for combined prophylaxis of PCP and toxoplasmic encephalitis (TE). They concluded that, although intolerance of dapsone and pyrimethamine was frequent, the once weekly dose was effective for primary prophylaxis of TE for patients who tolerated the regimen. Both regimens were found to be effective for prophylaxis against PCP.

In ACTG 154-ANRS 005²¹, a randomized double-blind study which compared the combination of 50 mg pyrimethamine and 15 mg folinic acid thrice weekly to placebo for primary prophylaxis of Toxoplasma encephalitis in 554 patients with HIV infection and CD4+ cell counts <200 cells/mm³, the rate of dose-limiting hematologic toxicity was 7% in the pyrimethamine group and 4% in the placebo group. This was not a statistically significant difference. Gastrointestinal toxicities occurred in 4% of the pyrimethamine group and 2% of the placebo group. Rash occurred in 7% of the pyrimethamine group and 1% of the placebo group; none of the patients developed life-threatening cutaneous reactions.

Pyrimethamine can cause hypersensitivity reactions at any dose, particularly when it is administered concomitantly with sulfonamides. Adverse reactions associated with pyrimethamine for treatment of toxoplasmosis (50 to 75 mg daily for adults) include anorexia, vomiting, megaloblastic anemia, leukopenia, thrombocytopenia, pancytopenia, atrophic glossitis, hematuria, and disorders of cardiac rhythm. Hematologic effects may occur at low doses in certain individuals.²²

Megaloblastic anemia associated with pyrimethamine is caused by pyrimethamine's folic acid antagonistic effect. Concurrent administration of folinic acid may prevent this toxicity. Allergic sensitization to folinic acid has also been reported.²³

Atovaquone Tablets for Treatment of PCP

Atovaquone has been shown to be safe and effective for the treatment of mild to moderate PCP in AIDS patients and is currently marketed in the U.S., Canada, and several European countries for patients who are intolerant of T/S. Clinical studies of the use of this agent for the treatment of malaria and for the treatment and suppression of cerebral and ocular Toxoplasma infection have also been conducted or are ongoing. Clinical studies of the safety and efficacy of atovaquone for prophylaxis against PCP had not been conducted prior to the present studies.

Three controlled clinical studies demonstrated the efficacy and safety of atovaquone tablets when administered orally as a therapy for AIDS patients with mild to moderate PCP.^{24 25 26} These studies demonstrated that atovaquone tablets were less effective than T/S and comparably effective to parenteral pentamidine for the treatment of AIDS patients with mild to moderate PCP. These studies also demonstrated that atovaquone is better tolerated by AIDS patients than either T/S or pentamidine, with only 11-14% of patients experiencing treatment-limiting adverse experiences. The most common adverse events reported by patients receiving atovaquone in these studies included rash, nausea, headache, diarrhea and mild elevations of liver function tests.

The mean steady-state plasma concentration of atovaquone achieved in patients enrolled in the T/S comparative trial was 14.0 ± 6.9 mcg/mL²⁷. The variability of plasma concentrations among patients in this trial was substantial, with as much as a 10-fold

difference in steady-state plasma concentrations observed among patients. A strong relationship between the effectiveness of atovaquone in curing PCP and the steady-state plasma concentrations was demonstrated, with a steady-state plasma concentration of 13.9 mcg/mL (95% CI = 11.9, 18.1 mcg/mL) predicted to result in a 90% probability of successful treatment.

Atovaquone Tablets for PCP Prophylaxis

Prior to the studies discussed in this review, formal clinical studies to assess the efficacy of atovaquone for the prevention of PCP had not been conducted. However, anecdotal information on the use of atovaquone tablets for PCP prophylaxis is available from other studies. As part of a pilot safety and efficacy trial (____-02) of atovaquone tablets in AIDS patients with mild to moderate PCP, six patients who had been successfully treated for their PCP with atovaquone, were allowed to continue on atovaquone at a dose of 750 mg once daily for 12 weeks to assess the safety of this agent. By 91 days, three of these patients experienced a relapse of PCP while receiving chronic atovaquone treatment. Plasma concentration data from other studies indicate that a dose of 750 mg of atovaquone tablets once daily would have achieved steady-state plasma concentrations of <10 mg/mL.²⁸

Thirty-one AIDS patients in a pharmacokinetic study (____-07) received various doses of atovaquone tablets. Five of the 31 patients developed PCP while participating in the ____ 07 trial. Atovaquone plasma concentrations ranged from 3.4 - 21.8 µg/mL.

Information on the occurrence of PCP was also collected in a clinical study of AIDS patients receiving atovaquone tablets for the treatment and suppression of *Toxoplasma encephalitis* (____ 02). In this trial, 93 patients with acute *Toxoplasma encephalitis* were treated with a dose of 750 mg atovaquone tablets four times daily. Of the 64 toxoplasmosis patients who did not receive other PCP prophylactic indications and for whom follow-up data are available, only one patient experienced PCP during a mean follow-up time of 124 days. These results would suggest an incidence of PCP of 4.6% per year at this dose. The average steady-state plasma concentration of atovaquone in patients receiving this dose of atovaquone tablets was 14.9 mcg/mL (range = 3.6 - 43.1 mcg/mL).²⁹

Atovaquone Suspension

Limited clinical experience has been obtained with the suspension formulation of atovaquone. This formulation has been shown to have better oral bioavailability than the tablet formulation. In a single-dose, cross-over pharmacokinetic study of the tablet and suspension formulations in healthy volunteers (study ____ 115), single doses of 750 mg atovaquone tablets (3 tablets) or 750 mg atovaquone suspension (5 mL) were administered to volunteers in a fasted and a fed state. The suspension formulation resulted in a 2.3-fold increase in C_{max} and a 2.2-fold increase in AUC. This study demonstrated that the suspension formulation had substantially greater oral bioavailability than the tablet formulation.

A Phase I study (115-201) was conducted to evaluate atovaquone suspension plasma levels with respect to inter- and intra-subject variability, dose-escalation, and concurrent administration with food.

Table 3 summarizes the preliminary pharmacokinetic results from this trial:

Table 3: Preliminary Results of Pharmacokinetic Study of Atovaquone Suspension in HIV-Infected Volunteers (201)				
Dose	Fasted		Fed	
	N	C _{SS} ^a , mcg/mL (range)	N	C _{SS} ^a , mcg/mL (range)
500 mg daily	21	6.8 (2.4-17.1)	20	11.4 (5.8-20.6)
750 mg daily	11	10.0 (3.0-27.1)	9	12.5 (5.1-21.7)
1000 mg daily	11	9.9 (4.4 - 15.9)	14	13.6 (6.4-26.0)
750 mg twice daily	-	-	5	21.1 (15.2-28.1)

^a C_{SS} = average steady-state plasma concentration.

In a Phase II study of atovaquone suspension for the treatment of mild to moderate PCP in patients with AIDS (202), 23 patients were treated with 750 mg atovaquone suspension twice daily with food (1500 mg total daily dose) for up to 21 days. These patients achieved an average steady-state plasma atovaquone concentration of 20.3 mcg/mL (range = 3.2-39.8 mcg/mL). An additional 6 patients received 1500 mg atovaquone suspension once daily. These patients achieved an average steady-state plasma concentration of 18.7 mcg/mL (range = 9.5-32.6 mcg/mL).

Atovaquone Dosage for PCP Prophylaxis

The optimal atovaquone plasma concentration for PCP prophylaxis is unknown; however, data from PCP treatment studies have demonstrated a direct relationship between steady-state plasma concentrations and successful therapy with atovaquone. In the T/S comparative study³⁰, 89 percent of patients who achieved a steady-state plasma concentration of at least 10 µg/mL were successfully treated with atovaquone. Also, 95 percent of patients who achieved a steady-state plasma concentration of at least 15 µg/mL were successfully treated.

Although it was not known if the direct relationship between plasma drug concentrations and efficacy observed for the treatment of PCP is relevant in choosing a dose for PCP prophylaxis, the dose chosen for this study was based on the objective of achieving steady-state plasma concentrations above 10 µg/mL. Data from studies 201 and 202 suggest that 1500 mg daily will achieve average steady-state plasma concentrations of approximately 20 µg/mL.

C. Emergence of resistance

Recent literature suggests but does not prove the development of atovaquone resistance via genetic shift (mutations resulting in amino acid changes in one of the ubiquinone binding sites). This occurred in 2/4 patients tested who had failed

prophylaxis.³¹ Please refer to the microbiologic review of Dr. Shukal Bala for a detailed discussion.

D. Overview of Clinical Development Program for PCP prophylaxis

Please refer to the subsequent tables for an overview of the clinical and PK studies. There were 3 studies included in this supplement. Two were clinical studies, and 1 was a pediatric PK study. Both clinical studies enrolled HIV-infected patients who had standard indications for PCP prophylaxis (CD4 lymphocyte count $<200/\text{mm}^3$ or a prior episode of PCP) and a history of intolerance to TMP/SMX.

Study 115-211

Study 115-211, conducted by the Terry Bein Community Program for Clinical Research on AIDS (CPCRA) in collaboration with the AIDS Clinical Trials Group (ACTG), compared atovaquone suspension, 1500 mg once daily, and dapsone tablets, 100 mg once daily, in 1057 patients.

Study 115-213

Study 115-213, conducted by the sponsor, compared atovaquone suspension, 1500 mg once daily, atovaquone suspension, 750 mg once daily, and aerosolized pentamidine, 300 mg once monthly, in 549 patients. Pharmacokinetic data was also collected.

ACTG 227 - Pediatric Pharmacokinetic Study

A completed pharmacokinetic study in pediatric patients (ACTG 227) compared steady-state plasma atovaquone concentrations in three age groups (2-13 years, 3-24 months and 1-3 months) after repeated oral administration of various doses of atovaquone suspension.

Ongoing Studies:

During the period in which these studies were conducted, five additional studies were initiated (two by the ACTG, one by the Agence Nationale de Recherches sur le SIDA (ANRS) and two by Glaxo Wellcome France). An ongoing study (ACTG 254) compares atovaquone suspension plus azithromycin versus TMP/SMX for prevention of serious bacterial infections and PCP in HIV-infected children. Two studies of atovaquone suspension for prophylaxis of *Toxoplasma* encephalitis (ACTG 237 and ANRS 047) were started in 1994 and 1995, respectively. Two studies to evaluate potential drug interactions between atovaquone suspension and rifabutin (MALB1001) or indinavir (MALB1003) were started in 1997.

Data from prior studies of a tablet formulation of atovaquone were previously submitted in NDA 20-259. Data from prior studies of MEPRON (atovaquone) Suspension were submitted in NDA 20-500. An overview of these studies is shown in tables 4 and 5.

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Table 4: Studies 115-211 and 115- 213

Study Number	Document No. and Report Location	Study Design	Treatments	Number of Subjects	Median Age in Years (Range)	Median Duration of Therapy in Months (Range)
115-211 (CPCRA 034, ACTG 277)	RM1997/00447	Randomized, open-label, controlled clinical trial in 1057 HIV-infected adult patients meeting criteria for PCP prophylaxis and intolerant to TMP/SMX	Atovaquone, 1500 mg daily	476 male 60 female	37 (12-73)	7.1 (0-30)
			Dapsone, 100 mg daily	450 male 71 female	37 (23-76)	7.2 (0-30)
115-213	RM1997/00594	Randomized, open-label, controlled clinical trial in 549 HIV-infected adult patients meeting criteria for PCP prophylaxis and intolerant to TMP/SMX	Atovaquone, 750 mg daily	171 male 17 female	37 (19-58)	6.2 (0-33)
			Atovaquone, 1500 mg daily	158 male 17 female	37 (25-64)	6.0 (0-34)
			Aerosolized pentamidine, 300 mg monthly	174 male 11 female 1 unknown	36 (19-68)	7.8 (0-33)

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Table 5: Pediatric PK study -ACTG 227 and Ongoing Studies

Study Number	Status	Study Design	Treatments	Number of Subjects	Age Range	Duration of Therapy
ACTG 227	Completed; manuscript in press	Phase I, dose-escalation, safety, tolerability, and pharmacokinetic study in HIV-positive infants and children.	Atovaquone, 10 mg/kg/d Atovaquone, 30 mg/kg/d Atovaquone, 45 mg/kg/d	27 total	1 month to 12 years	12 days
ACTG 254	Ongoing study	Randomized, double-blind, controlled clinical trial of bacterial and PCP prophylaxis in HIV-infected infants, children and adolescents	Atovaquone, 30 mg/kg/d plus Azithromycin, 5 mg/kg/d TMP/SMX, 5/25 mg/kg/d	Target 580 322 enrolled as of 13 Aug 97	3 months to 19 years	indefinite (range 0-97 weeks as of 13 Aug 97)
ACTG 237	Ongoing study	Randomized, open-label, controlled clinical trial in HIV-infected patients with <i>Toxoplasma</i> encephalitis	Atovaquone, 1500 mg bid plus either Sulfadoxine, 1-1.5g qid or Pyrimethamine, 50-75 mg qd plus Folinic acid, 10 mg qd	Target 100 49 enrolled during 27 months	≥13 years	indefinite
ANRS 047	Ongoing study	Randomized, open-label, controlled clinical trial of toxoplasmosis prophylaxis in HIV-infected patients	Atovaquone, 1500 mg/d Pyrimethamine, 50 mg 3x/wk plus Folinic acid, 15 mg 3x/wk	Target 500 101 enrolled as of 31 Mar 97	≥15 years	indefinite
MALB 1001	Ongoing study	Open-label, 3-way cross-over, drug interaction study in 24 healthy volunteers	Atovaquone, 750 mg bid Rifabutin, 300 mg qd	24	adults	14 days each treatment alone and combined
MALB 1003	Ongoing study	Open-label, 3-way cross-over, drug interaction study in 24 healthy volunteers	Atovaquone, 750 mg bid Indinavir, 800 mg tid	24	adults	14 days each treatment alone and combined

II. A Randomized, Comparative Study of Daily Dapsone and Daily Atovaquone for Prophylaxis Against PCP in HIV-Infected Patients who are Intolerant of Trimethoprim and/or Sulfonamides

Study 115-211

1. OBJECTIVES

Primary Objective

To compare the efficacy and safety of two regimens—dapsone (100 mg/day) and atovaquone (1500 mg/day)—in preventing or delaying the onset of histologically proven or probable PCP in T/S-intolerant, HIV-infected patients with CD4+ cell counts of <200 mm^3 or <15 percent of the total lymphocyte count, and in preventing or delaying the recurrence of PCP in individuals who have experienced previous episodes.

Secondary Objectives

1. To compare the toxicities of the two regimens.
2. To compare the incidence of the combined endpoint of PCP, extrapulmonary pneumocystosis, and death in the two treatment arms.
3. To compare the incidence of toxoplasmosis in the two treatment arms.
4. To compare the mortality rates in the two treatment arms.

2. STUDY DESIGN

This was a multicenter, randomized, open-label, comparative study of two prophylactic regimens (daily dapsone and daily atovaquone) in HIV-infected patients with either a history of PCP or a CD4+ cell count of $<200/\text{mm}^3$ or <15 percent of the total lymphocyte count, who are intolerant of trimethoprim and/or sulfonamides. Patients who developed a severe or persistent study drug toxicity that resulted in permanent discontinuation of the assigned study drug were switched to the alternate regimen. Those who developed PCP while on their assigned study drug could continue on the assigned study drug or be switched to the alternate study drug at the clinician's discretion. The average follow-up period was expected to be 24 months. The duration of the study was approximately 30 months.

3. MATERIALS AND METHODS

Patient Selection

Medical Officer's Note: All investigators in this study were enrolled by CPCRA. The Applicant is unsure if CPCRA compared investigator names to the FDA's list of restricted investigators prior to their enrollment. Patient numbers by study site is presented in Appendix 1.

Eligible Patients

- The eligibility criteria were designed to include all patients for whom a primary care physician would prescribe PCP prophylaxis and to exclude some patients for safety reasons.
- The patient must have met all of the inclusion criteria and could not have any of the conditions that would exclude him or her from the study.
- Patients with the following laboratory values were considered to have adequate organ function for entry into the study:
 - Hemoglobin > 7.0 g/dL
 - Platelet count > 50,000/mm³
 - Absolute neutrophil count > 750/mm³
 - AST or SGOT level < 5 x the upper limit of normal
 - Total bilirubin level < 2.5 mg/dL

NOTE: If the patient's laboratory values did not meet these recommended levels, the clinician could use his or her clinical judgment to determine whether or not the patient had adequate organ function for participation in this study.

- Pregnant patients could be included at the clinician's discretion.
- Patients who were already receiving PCP prophylaxis could enter the study if they were willing to discontinue the nonstudy prophylactic medication once study drug was provided.

Intolerance to Trimethoprim and/or Sulfonamides

For this study, patients were considered to be intolerant of trimethoprim and/or sulfonamides if they had a history of reaction to trimethoprim and/or sulfonamides (e.g., allergic/skin reactions; gastrointestinal symptoms; hematologic, renal, neurologic, or hepatic complications, etc.) that required the permanent discontinuation of either medication.

Inclusion Criteria

1. A working diagnosis of HIV infection based on the patient's medical history, behavioral history, clinical signs and symptoms, or results of laboratory tests.
2. CD4+ cell count of either < 200 cells/mm³ or < 15 percent of the total lymphocyte count at any time in the past OR history of PCP.
3. History of intolerance of trimethoprim and/or sulfonamides.
4. Age > 13 years.
5. Adequate G6PD (normal or elevated).
6. Patient (or guardian) had signed an informed consent form.

Exclusion Criteria

1. Known treatment-limiting reaction to dapsone or atovaquone.
2. Continued use of any medication (other than study drug) with potential anti-PCP activity or anti-PCP placebo after study drug is dispensed
3. Active pneumocystosis.

Medical Officer's Note: The inclusion and exclusion criteria are acceptable.

Randomization, Sample Size and Statistical Considerations

Patients were randomized evenly to one of the two prophylactic regimens. Patients were stratified according to history of PCP and *Toxoplasma* serology results.

Within each unit, the study patients were equally randomized by PCP status (primary or secondary prophylaxis) and *Toxoplasma* serology results (positive or negative) to one of the two treatment arms. Data were formally monitored at 6-month intervals, or more frequently as necessary, until the conclusion of the study.

PCP incidence rates in the CPCRA Observational Data Base and information from published and unpublished studies were considered in determining the sample size. Rates for PCP incidence for patients receiving dapsone were computed by type of prophylaxis (primary or secondary). Sample size calculations were made for the PCP endpoint, with death considered a censoring event. For the purposes of these calculations, rates for dapsone were considered as the standard.

The 2-year rates of PCP for dapsone were assumed to be 20 percent for primary prophylaxis and 40 percent for secondary prophylaxis. The crossover rate from dapsone to atovaquone was assumed to be 35 percent. The crossover rate from atovaquone to dapsone was assumed to be 15 percent.

For the PCP endpoint, censoring events included mortality and loss to follow-up. Mortality rates were assumed to be 20 percent and 40 percent for the primary and secondary groups, respectively. For the PCP endpoint, loss-to follow-up rates were assumed to be 10 percent of the surviving individuals (or 8.0 percent and 6.0 percent overall for the primary and secondary groups, respectively).

Therefore, a total sample size of 700 patients was required. A sample size of 350 patients per treatment arm would provide 80 percent power to detect a 50% reduction in the PCP rate.

Statistical Reviewer's Note: The sample size per treatment arm in the completed study was greater than the sample size stated above. Thus, given the assumptions above to be true, the study should have been sufficiently powered to detect a 50% reduction of PCP incidence for atovaquone in comparison to dapsone.

Patient Monitoring and Follow-up

- Patients were seen in the clinic for routine follow-up clinical evaluations as necessary and for study visits every 4 months. Patients were monitored for signs and symptoms of study drug toxicity or infection, and diagnostic work-up was performed as necessary. Diagnostic evaluation for suspected study endpoints was pursued.
- Clinicians were allowed to switch patients to the alternate study arm. A patient who switched to the alternate arm continued to be clinically assessed as necessary and for study visits every 4 months. Patients who were permanently withdrawn from all study therapy continued to be clinically assessed every 4 months.
- It was recommended that patients who were *Toxoplasma* seropositive with CD4+ cell counts between 100 and 200 cells/mm³, and who were receiving dapsone (either by

assignment or switchover) have CD4+ cell counts monitored every 4 months and that pyrimethamine and folinic acid should be added to their regimens if their CD4+ cell counts dropped below 100 cells/mm³.

- Patients who received dapsone and pyrimethamine as study medications and who developed intolerance to pyrimethamine could continue on dapsone alone.

Development of Opportunistic Infections

Medical Officer's Note: The following were suggestions for managing opportunistic infections. Actual work-up and care was left to the treating clinician's discretion.

1. Patients with symptoms suggestive of an intercurrent opportunistic infection should be evaluated with blood cultures and other cultures for bacterial and fungal pathogens as clinically indicated.
 - It was recommended that patients with symptoms suggestive of PCP and/or other pneumonia have a chest x ray, sputum examination, and arterial blood-gas determination. A gallium scan should be considered. If any of these tests were abnormal, a bronchoscopy should be performed (unless the diagnosis is made by induced sputum examination).
 - The investigator was referred to the *CPCRA Investigator's Handbook* for guidelines for the work-up of other suspected opportunistic infections.

If either confirmed or probable *Pneumocystis carinii* infection was documented, the clinician could either resume the originally assigned study therapy or switch the patient to the alternate study therapy after treatment of the acute episode was completed. If the clinician decided to neither resume the originally assigned therapy nor follow the switchover format, the patient was permanently withdrawn from study therapy. The patient continued to be followed according to study guidelines until study completion.

2. If the patient developed an opportunistic infection (e.g., a bacterial infection) that required the initiation of treatment with a medication that had potential anti-PCP activity, the patient could, at the physician's discretion, be temporarily removed from study medication. If the patient was temporarily removed from study medication, study therapy was resumed when the medication with potential anti-PCP activity was discontinued. The patient continued to be followed according to study guidelines.

Pregnancy

Women who became pregnant while receiving dapsone or atovaquone could, at the clinician's discretion, be temporarily removed from study medication during certain periods of the pregnancy and the postpartum period, including the first trimester and the period from the 38th week of pregnancy through delivery or through the second postpartum month, if the women were breastfeeding. It was recommended that these women receive PCP prophylaxis with aerosolized pentamidine while off study medication (see Criteria for Discontinuation of Study Medication section).